

Revisiting the role on antiepileptic drugs in idiopathic childhood epilepsy- an observational outcomes study in Eastern India

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Abstract

Introduction: Seizures constitute the most common neurological disorder in children and the majority of epilepsy has its onset in childhood. Epilepsy, particularly childhood epilepsy, remains a challenge to treat. Despite the increase in the number of antiepileptic drugs (AEDs), more than 25% of children with idiopathic childhood epilepsy continue to have seizures. In spite of continued emergence of newer drugs, the response to antiepileptic therapy is still unpredictable and unsatisfactory. The physicians and even the neurologists are in a dilemma and vary from one another in selecting the most appropriate drug in a particular type of epilepsy. Monotherapy is the usual dictum, but polytherapy is needed for patients with multiple seizure types or refractory disease. It is felt, therefore, necessary to know the prevalence of various types of childhood epilepsy and the prescribing pattern of antiepileptic drugs. **Objectives:** The study was conducted to evaluate the prescribing pattern of antiepileptic drugs in different types of idiopathic childhood epilepsy and to compare the efficacy and safety profile of commonly used AEDs. **Methodology:** A total of 100 Idiopathic epileptic patients of both sexes below 18 yrs of age who were prescribed AEDs were considered for analysis. Demographic profile, type of epilepsy, AEDs, number of epileptic events, biochemical, EEG and ADR (Adverse drug reaction) data were collected and analyzed. **Results:** A total of 100 subjects were analyzed, of whom 56% were male. The mean age at onset of epilepsy was 5.5 years. Incidence of Generalized Tonic-Clonic Seizure (GTCS) was 79%, Complex Partial Seizure 63%, Partial Seizure with Secondary Generalization 32%, Simple Partial Seizure 8%, Myoclonic 8%, Absence 7% and Atonic 5%. Valproate was the most commonly prescribed drug in GTCS, Atonic, Myoclonic and Absence seizure. Carbamazepine was commonly prescribed drug in Partial seizure. A total of 110 AEDs (i.e.1.1 AED per patient) were prescribed. The majority of subjects (90%) required monotherapy. Overall, only 6% patients received newer AED and majority of patients (94%) were on older AED therapy. Valproate achieved fastest seizure control in 95% of children within three months whereas Carbamazepine and Phenytoin required six months of therapy to achieve the same extent of seizure control. Major adverse events that resulted in cessation of antiepileptic medication were reported in 3 (3%) subjects. Two (2%) patients treated with carbamazepine had major adverse events that include rash (2patient). One (1%) patients treated with valproate develop weight gain (1patient). One (1%) patient treated with phenytoin had gum hyperplasia. One (1%) patients treated with phenytoin had major adverse events that include ataxia and nystagmus. **Conclusion:** Idiopathic childhood epilepsy was more common in male children of mean age of 5.5year. GTCS was the commonest type of epilepsy. The majority of epileptic children received monotherapy and older AEDs. Valproate was the commonly prescribed drug in all type of epilepsy other than Partial seizure. It was the most effective and safe drug compared to other AEDs.

Keywords: Antiepileptic drugs, Idiopathic childhood epilepsy

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Introduction

Seizures constitute the most common neurological disorder in children and the majority of epilepsy has its onset in childhood. The

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tendency for recurrent seizures characterizes epilepsy, which is a group of heterogeneous and chronic neurological disorders operationally defined by the occurrence of two or more unprovoked seizures [1]. Recently, the International League against Epilepsy (ILAE) defined epilepsy as 'a brain disorder characterized by a predisposition to generate epileptic seizures and requires the

occurrence of at least one epileptic seizure' [2]. The ILAE stratified seizures into partial, generalized and unclassified seizures [3]. Partial onset seizures are characterized by seizures that initially involve a localized cortical area, from which it may subsequently propagate to involve other brain regions. Generalized onset seizures, by contrast, from the start involve both hemispheres simultaneously or nearly simultaneously [4]. Epilepsy, particularly childhood epilepsy, remains a challenge to treat. Despite the increase in the number of antiepileptic drugs (AEDs), more than 25% of children with childhood epilepsy continue to have seizures [5]. There are some special problems in the treatment of childhood epilepsy as they are more susceptible to the hepatotoxic effect of valproic acid and phenobarbitone induced alteration of behavior and impairment of learning process [6]. In spite of continued emergence of newer drugs, the response to antiepileptic therapy is still unpredictable and unsatisfactory. The physicians and even the neurologists are in a dilemma and vary from one another in selecting the most appropriate drug in a particular type of epilepsy. Monotherapy is the usual dictum, but polytherapy is needed for patients with multiple seizure types or refractory disease [7]. It is felt, therefore, necessary to know the prevalence of various types of childhood epilepsy and the prescribing pattern of antiepileptic drugs. Prior to 1993, the choice of AEDs was limited to old antiepileptic drugs (AEDs) (phenobarbital, primidone, phenytoin, carbamazepine, valproate and ethosuximide). Among them, valproate, carbamazepine and Phenobarbital are effective and more widely used medications for the treatment of many types of epilepsy [8]. Since 1993, 11 new AEDs (felbamate, oxcarbazepine, gabapentin, lamotrigine, topiramate, levetiracetam, tiagabine, vigabatrin, pregabalin, rufinamide, zonisamide, and lacosamide) have been introduced to the market. Because of the lack of data on the efficacy and safety of the new AEDs, their applications depend on the clinicians' own experiences. Levetiracetam and oxcarbazepine are the new generation AEDs that are increasingly used as monotherapy as well as add-on therapy in children [9, 10]. However, treatment failure due to lack of seizure control or intolerable adverse effects remains the major consequences in children suffering from epilepsy. The pharmacokinetics of AEDs in pediatric population differs considerably from those of adults [11]. Although it has been suggested that the efficacy of AEDs in adults could be used to predict the efficacy of AEDs in the pediatric population [12], effectiveness of old and new AEDs in everyday child neurology practice has not been well-described, likely due to legal and ethical restrictions in performing randomized controlled trials establishing the efficacy of a new AEDs well-described, likely due to legal and ethical restrictions in performing randomized controlled trials establishing the efficacy of a new AED. It requires long-term medication in children. Periods of remission and relapse may interchange. Such a dynamic course might influence our interpretation of the results of prognostic studies, advice to patients and treatment strategies. It is therefore prudent to attach importance on efficacy and safety of the AEDs.

Aim and Objectives

Generalized objective: In the present study, we aimed to investigate the efficacy and tolerability of old and new AEDs in children with newly diagnosed idiopathic epilepsy when used as a first-line treatment.

Specific objectives

- To evaluate the prescribing pattern of antiepileptic drugs in different types of idiopathic childhood epilepsy.
- To compare the efficacy and safety profile of commonly used AEDs

Methodology

The observational prospective study was conducted at Clinical & Experimental Pharmacology, School of Tropical Medicine, Kolkata (STM) [01.03.2017 to 30.10.2018] where the planning, overall conduct, monitoring, and data management were done. Collection of relevant data was done at the out-patients department of Pediatric medicine in Medical College and Hospital, Kolkata (MCH).

Enrolment of patients commenced after having obtained the approval from the institutional ethics committees of the two institutes. The diagnosis was confirmed by a pediatrician along with consultation with neurologist as and when required. Case categorization was done on the basis of clinical presentation of seizure, supported by electroencephalography (EEG) and radio imaging study on selected cases. A total of 110 patients were approached, of whom 100 given assent (where applicable) and consent to participate in the study. We excluded all surgical causes of convulsion, febrile convulsion, cerebral palsy and patients with status epilepticus and epileptic syndrome.

Study Variables

1. Type of epilepsy
2. Prescribing pattern of AEDs
3. Drug related information like:

- *Generic name of drugs*
- *Monotherapy or polytherapy*

The information was compiled and the distribution pattern of various clinical types of epilepsy in relation to age and sex and the incidence of prescription of individual antiepileptic agent was calculated. Patients were considered to be seizure-free if they had no more seizures for at least 12 months on a stable dose in monotherapy or breakthrough seizures only with missed doses of medication. A first-drug treatment failure was defined discontinuation of the AED due to lack of seizure control despite being able to tolerate the medication in maximum doses (lack of efficacy), or intolerable adverse events. Adverse events were classified as major and minor events according to their severity. Major adverse events were defined as events leading to cessation of AEDs. Adverse events which were tolerated by modification of the dosing scheme, symptomatic or supportive management, or behavioral modification were considered minor adverse events. Adverse psychiatric events including irritability, hyperactivity, agitation, and aggressive behavior were grouped as behavioral or personality changes. Children were monitored at the first month after the beginning of drug therapy and at every three months subsequently. At each visit, seizure response, adverse events, medication dose and duration of use, the reason for medication discontinuation, and adherence were recorded. Adverse drug reaction (ADR) profile includes:

1. The incidence and type of adverse drug reaction
2. The causality assessment of the ADR with suspected drug according to WHO-UMC ADR probability scale
3. Whether the suspected drug was stopped after the ADR
4. Whether any treatment was given for the ADR
5. The drug(s) most commonly causing ADRs

Statistical Analysis: Data generated from this study was analyzed by Graph Pad Instat. As appropriate, paired t test and one-way Analysis of Variance [ANOVA] with post-hoc test Dunnet multiple comparison test was used to assess the statistical significance of differences in means (p values <0.05 were considered significant).

Results

A total of 100 subjects were analyzed, of whom 56% were male. The mean age at onset of epilepsy was 5.5 years. Distribution according to the type of epilepsy was shown in Table 1. The pattern of AEDs prescribed and the different therapeutic approaches of epilepsy treatment utilized are presented in Tables 2. Regarding the treatment, the majority of epileptic children received monotherapy (90%) and only a small percentage of patients (10%) required polytherapy for the control of seizures. The majority of epileptic children received valproate (74%), which was followed by carbamazepine (12%) and phenytoin (10%). Again valproate is the most common agent with other drug as combination. Only a small percentage of subjects received lamotrigine & levetiracetam (2 subjects each), topiramate (1 subject) and oxcarbamazepine (1 subject). Most common add on AEDs were clobazam and clonazepam in case of complex partial seizure. Maximum AEDs prescribed in generic name (95%). Efficacy of commonly used AEDs like valproate, carbamazepine and

phenytoin in the prevention of idiopathic epileptic seizure is depicted in Table 3. Five out of 100 reported ADRs (5%) as shown in the Table 4. Major adverse events that resulted in cessation of antiepileptic medication were reported in 3 (3%) subjects. Two (2%) patients treated with carbamazepine had major adverse events that

include rash (2 patients) required stoppage of that medicine. One (1%) patients treated with valproate develop weight gain (1 patient). One (1%) patient treated with phenytoin had gum hyperplasia. One (1%) patients treated with phenytoin had major adverse events such as ataxia and nystagmus, required withdrawal of that medicine.

Table 1: Distribution according to the type of epilepsy

Type of epilepsy (n=100)	Sub-type of epilepsy	No. of patients (%)
Primary Generalized Seizure (n=73)	a) Tonic clonic	58 (79)
	b) Tonic	0 (0)
	c) Atonic	4 (5)
	d) Absence	5 (7)
	e) Myoclonic	6 (8)
Partial Seizure (n=27)	a) Simple partial	2 (8)
	b) Complex partial	17 (63)
	c) Partial seizure with secondary generalization	8 (32)

Table 2: Prescribing pattern of AEDs

Type of therapy	No (%)
Most frequent add on AEDs (n= 10)	
Clobazam	4(40)
Clonazepam	6(60)
Most frequent AEDs as monotherapy (n= 90)	
Valproate	75(80)
Carbamazepine	9(10)
Phenytoin	6(7)
Overall AEDs utilization (Total AED= 110)	
Valproate	81(74)
Carbamazepin	12(11)
Phenytoin	11(10)
Levetiracetam	2(2)
Lamotrigine	2(2)
Oxcarbamazepine	1(1)
Topiramate	1(1)

Table 3: Efficacy of valproate, carbamazepine and phenytoin in the prevention seizure

Duration of therapy	No of epileptic seizures/month		
	Valproate (Mean ± SEM) [n=74]	Carbamazepine(Mean ± SEM) [n=14]	Phenytoin (Mean ± SEM) [n=11]
Baseline	4.99 ±0.63	4.14 ± 0.93	4.82 ±0.91
After 1 month	1.42 ±0.49*	1.50 ± 0.25*	2.18 ±0.55**
After 3 months	0.07 ±0.04*	0.57 ± 0.17*	1.00 ±0.38*
After 6 months	0.05 ±0.01*	0.24 ± 0.09*	0.75 ±0.15*

*p <0.001, **p<0.01 when compared to the respective control

Table 4: Adverse drug reactions

No. of Patients ADR reported	Suspected drugs	Causality assessment	Whether treatment with AED continued/stopped
1-Weight gain	Valproate	Possible	Continued
1- Gum hyperplasia	Phenytoin	Possible	Continued
1- Decreased memory and learning	Carbamazepine	Possible	Stopped
2- Rash	Carbamazepine	Probable	Stopped
1-Ataxia & nystagmus	Phenytoin	Probable	Stopped

Discussion The current study attempts to analyze the pattern of drug prescribing in different types of epilepsy. The majority of epileptic

children received monotherapy and only a small percentage of patients required polytherapy for the control of seizures. It is also felt

that India being a developing country, a large section of people live below the poverty line. Naturally the cost of treatment produces a substantial financial burden to the family. This financial constraint is one of the important causes for poor patient compliance with the antiepileptic drug therapy. It is therefore prudent to attach importance not only on efficacy and safety of the drugs, but also on daily or monthly cost of therapy. It would ultimately help to constitute an institutional Essential Drugs List and institutional treatment guideline of childhood epilepsy in terms of efficacy, safety, suitability and cost of antiepileptic drug therapy. It may be of immense help in the clinical management of epilepsy in the Government hospital of West Bengal. Valproate was the most commonly prescribed drug in GTCS, atonic, myoclonic and absence seizure. Carbamazepine was commonly prescribed drug in Partial seizure. It was further observed that majority of epileptic children received the antiepileptic drugs in generic name and in tablet form. The ultimate outcome of AEDs treatment in paediatric epilepsy is to attain no seizures and no or minor side effects. Fortunately, this goal is often met by using appropriate AEDs as monotherapy. Our data indicated that monotherapy was the therapy of choice in majority of patient with partial or generalized seizure. This finding correlated with the finding in other studies [13-16]. The reason for polytherapy may be attributed to higher incidence of refractory epilepsy in any study. Polytherapy increases the potential for drug-drug interaction, can increase the risk of chronic toxicity and is associated with a higher cost of medication. However, in polytherapy there is improved seizure control Only 5(5%) patients reported ADRs. Among all the commonly prescribed antiepileptic drugs valproate, phenytoin produced side effects which were mild; dose relate. The selection of 'P' drugs for various types of epilepsy should be based on efficacy, safety, suitability and cost. In our study, we observed 6% prescription of newer AEDs [17]. Major adverse events that resulted in cessation of antiepileptic medication were reported in 3 (3%) subjects. Three (3%) patients treated with carbamazepine had major adverse events that include behavioral problems (1patients), rash (2 patients). All the adverse events and SAEs were reported to the local ADR monitoring centre under the pharmacovigilance programme of India (PvPI). Causality assessment using WHO UMC causality assessment scale revealed that only 3% ADRs were under probable category, while rest was possible. Valproate achieved fastest seizure control in 95% of children within three months whereas Carbamazepine and Phenytoin required six months of therapy to achieve the same extent of seizure control (Table 3). By comparing efficacy analysis among all the AEDs, it is observed that valproate is the most effective antiepileptic drug.

Conclusion

Idiopathic childhood epilepsy was more common in male children. The mean age at onset of epilepsy was 5.5 years. GTCS was the commonest type of epilepsy. The majority of epileptic children received monotherapy and older AEDs. Valproate was the commonly prescribed drug in all type of epilepsy other than partial seizure. It was the most cost effective and safest AED. The study was conducted in a very small number of patients. The study was conducted for 18 months and not beyond that. If the study can be extended further by collecting the data for comparing the efficacy and the toxicity profile of the drugs from a sufficient number of patients from the aforesaid as well as the other tertiary care hospitals, it may be possible to resolve the long continued dispute of selecting the most appropriate

drugs in a particular type of epilepsy. Knowledge of the long-term outcome of epilepsy is of the utmost importance in the treatment of children with epilepsy. It is still largely unknown whether the long term outcome of epilepsy is determined by its natural course or whether it can be modified by treatment. Long-term follow up studies may be helpful to solve this dispute.

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